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2nd May 2014

Dear Sirs

We are current planning for a REACH registration for n-Butanol (71-36-3) for 2018. I have been directed to yourself with regard to access to a number of studies used to the earlier REACH registration. These studies are:

7.5.1 Repeated dose toxicity oral

Reference type	Author	Year	Title	Bibliographic source	Testing laboratory	Report no.	Owner company	Company study no.	Report date
study report	US EPA	1986	Rat oral subchronic toxicity study of normal butanol.	TRL Study #032-006	Toxicity Research Laboratories Ltd.	032-006	USEPA Research Triangle Institute		

7.8.1 Toxicity to reproduction

Reference type	Author	Year	Title	Bibliographic source	Testing laboratory	Report no.	Owner company	Company study no.	Report date
study report	Toxicity Research Laboratories Ltd.	1986	Rat oral subchronic toxicity study of normal butanol.	TRL Study #032-006	Toxicity Research Laboratories Ltd.	032-006	USEPA Research Triangle Institute		

Can you please provide information as to what would be required in order to obtain access to use these studies for our own REACH registration under the BASF lead registration. In particular we are interested in timescales and costs.

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Chemical Category		
N-BUTANOL		

U.S. EPA 1986a

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2/20/86

TRI STUDY #032-006

Conducted for:

n-Butanol OFD

RESEARCH TRIANGLE INSTITUTE
P.O. Box 12194
Research Triangle Park, North Carolina 27709

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by:

TOXICITY RESEARCH LABORATORIES, LTD.
510 West Hackley Avenue
Muskegon, Michigan 49444

Rat Oral Subchronic Toxicity Study

Compound:

Normal Butanol

conclusion

On p. 15

I see nothing
that changes

the conclusion

npd

5-14-86

Start of Test (pretreatment):

August 19, 1985

Interim Necropsy:

October 7 and 8, 1985

Final Necropsy:

November 25 and 26, 1985

SUMMARY

The purpose of the study was to evaluate the toxicity of normal butanol in a rat subchronic toxicity study.

Four groups of male and female rats (30/sex/group) were dosed orally once daily with 0, 30, 125, or 500 mg/kg/day of compound for 6 weeks until the day of the interim necropsy. After the interim sacrifice, all surviving rats were dosed daily until the final sacrifice. Body weights and food consumption were recorded weekly and the rats were observed at least twice daily for mortality and overt signs of toxicity. Ophthalmologic examinations were done during the pretreatment period and again during week 13. Blood and urine for clinicopathologic evaluation were collected from a fifth group of 10 rats/sex prior to initiation of dosing, from all surviving rats scheduled for the interim sacrifice, and from the first 10 rats/sex/group at the final sacrifice. The first 10 male and 10 female rats from each group were scheduled for necropsy on day 43 or 44 and all remaining rats on day 92 or 93. Gross postmortem examinations were done on all rats. Organ weights were taken from rats sacrificed on day 92 or 93. After the final sacrifice, a complete histopathologic examination was done on all rats in the control and high-dose groups, on livers, kidneys, and hearts from the low- and mid-dose groups, and on all gross lesions. In addition, a histopathologic examination was done on any rat found dead or sacrificed in extremis.

The only unequivocal effects produced by normal butanol were ataxic and

hypoactivity at the 500 mg/kg/day dose level. The maximum weekly incidence was 32% and 29%, respectively, but ataxia or hypoactivity were not seen as treatment-related signs until the final six weeks of the study. No treatment-related clinical signs were seen at the 30 or the 125 mg/kg/day dose level.

Body weight and food consumption values were similar for control and all treated groups. No treatment-related effect was observed at the ophthalmoscopic examinations or in gross or microscopic evaluation of the tissues.

Three rats were found dead or sacrificed in extremis, but these deaths were not due to administration of the normal butanol.

At the interim clinical pathologic evaluation, red blood cell count (RBC), packed cell volume (PCV), and hemoglobin (HGB) averages of the 500 mg/kg/day dose group females were 5% below control averages. Although these differences were statistically significant, they were small and no differences between the parameters were observed in the males of the interim evaluation or between control and treated groups of either sex at the final evaluation. Therefore, even if the lower red blood cell parameters in the 500 mg/kg/day females were an actual treatment-related effect, it was small and transitory.

CONCLUSION

Oral administration of normal butanol at 500 mg/kg/day produced ataxia

and hypoactivity at a maximum weekly incidence rate of 32 and 29%, respectively. A slightly (5%) lower (compared to controls) red blood cell count (RBC), packed cell volume (PCV), and hemoglobin (HGB) concentration present in the 500 mg/kg/day dose group females at the interim evaluation only may have been treatment-related.

No treatment-related effect was observed at the 30 mg/kg/day or 125 mg/kg/day dose levels.

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TR Study #032-006

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Appendix C Clinical Pathology Methodology
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Appendix E Histoaccountability Report
Appendix F Protocol and Amendments.
Appendix G QAU Statement

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I Introduction

The purpose of this study was to evaluate the toxicity of normal butanol in a rat subchronic toxicity study. In order to assess the toxicologic potential after both 6 weeks and 13 weeks of dosing, an interim sacrifice at the 6 week interval was included.^a The oral route of administration was used because this is the probable route of human exposure.

This study was conducted in accordance with the protocol (Appendix F), the Standard Operating Procedures of Toxicity Research Laboratories (TRL) and in compliance with Good Laboratory Practice Regulations for Nonclinical Laboratory Studies.^b Procedures pertinent to this study are described herein.

II Methods

A. Test Material

Normal butanol (lot # 3597 KVVE) was purchased from American Scientific Products, Romulus, Michigan. Samples of each dose concentration were saved during weeks 1, 4, 6, 10, and 13 and taken to the Muskegon County Wastewater Treatment Facility for chemical analysis at the laboratory under the direction of Dr. Avi Joshi, Physical Chemist. Duplicate samples were sent to Mr. John Maney, ERCO, a division of Enseco, Inc., 185 Alewife Brook Parkway, Cambridge, Massachusetts for referee analysis.

^a Protocol Change #4, effective 9/10/85.

^b Federal Register, Vol. 43, No. 247, Part 11, December 22, 1978, pp. 59985-60020.

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B. Animals and Husbandry

The rat was chosen as a test system because of its established usefulness in toxicologic studies and as a pharmacologic model. One hundred-fifty three male and one hundred-forty seven female rats^a (45-55 grams) aged 22-23 days arrived on August 12, 1985 and were housed individually in wire-bottom cages^b. Filtered municipal water^c and Purina Certified Rodent Laboratory Chow^d were available ad libitum. This feed has been tested by the manufacturer for contaminants, none of which were present at levels that would be expected to affect the outcome of the study. An acclimation period of 7 days prior to the pretreatment week was allowed. During the acclimation period, the rats were observed with respect to general health and any rat with evidence of disease or physical abnormality was discarded. A clean/dirty corridor system was in effect. Room air was filtered and humidity (average 47.6%, \pm 9.2) and temperature (average 70.2°F, \pm 2.2) controlled. The temperature value was calculated using the daily high and low value, \pm 1 standard deviation. One value per day was used to calculate the humidity average. A 12 hour light:12 hour dark cycle was controlled automatically.

^a Charles River Breeding Laboratories, Inc., Portage, Michigan. Cr1: CD^R(SD)BR.

^b Rats were housed in accordance with recommendations contained in DHEW Publication No. 78-23 (NIH): Revised 1978, "Guide for the Care and Use of Laboratory Animals." During the acclimation period the rats were housed 3/cage.

^c Water used at TRL analyzed periodically for the presence of contaminants as defined by the Environmental Protection Agency "National Interim Primary Drinking Water Regulations" Code of Federal Regulation, Title 40-Protection of Environment Part 141.11 (b) and 141.12. Records retained at TRL.

^d Lot #s May02-85-3E, Aug01-85-2E, Aug07-85-1B, Aug10-85-2D, Aug21-85-2D, Purina Lab Chow-12T, Checkerboard Square, St. Louis, MO 63108.

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The first day of the pretreatment week was August 19, 1985. At the initiation of the pretreatment week the rats were assigned randomly to groups (30 rats/sex/group and a fifth group of 10/sex) using a computer printout.^a The rats were individually identified by toe clipping.

C. Compound Administration

Administration of the test material began on August 26, 1985. The rats scheduled for the interim sacrifice were dosed daily for 42 or 43 days and the rats scheduled for the final sacrifice were dosed daily for 91 or 92 days.

Group	Normal Butanol (mg/kg/day)	Animal Numbers			
		Interim	Male	Interim	Female
I	0	001-010	Final	011-030	031-040
II	30	061-070	Final	071-090	091-100
III	125	121-130	Final	131-150	151-160
IV	500	181-190	Final	191-210	211-220
V	Baseline	241-250			251-260

The amounts administered were based on individual weekly body weight values. Fresh solutions of the compound (in deionized water) were prepared weekly and dosed orally at a volume of 10 ml/kg. Controls received deionized water at the same volume. A plastic syringe and an 18 gauge ball-tipped metal dosing cannula ensheathed in a number 8 French catheter were used to administer the solution.

^a Randomization printout programmed by Dr. John Quiring, Associate Professor of Mathematics and Computer Science, Department of Mathematics and Computer Science, Grand Valley State Colleges, Allendale, Michigan.

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D. Clinical Observations

Body weights and food consumptions were recorded weekly and the rats were observed at least twice daily for mortality and clinical effects.

E. Ophthalmology

All rats received an ophthalmoscopic examination during the pretreatment period and week 13 by a veterinary ophthalmologist^a. Ophthalmologic examinations were conducted on all rats in a darkened room with an indirect ophthalmoscope. Seven rats that had an eye lesion during the pretreatment period were not included in the study.

F. Clinical Pathology

1. Sampling

Blood and urine samples were collected from the 10 male and 10 female rats in group V prior to initiation of dosing. Blood was obtained at the time of necropsy from all surviving rats scheduled for the interim sacrifice and from the first ten rats/sex/group at the final sacrifice. Urine was collected in metabolism cages 3-5 days prior to the scheduled sacrifices. The rats were anesthetized with CO₂, the thoracic cavity was opened and blood was collected by cardiac puncture. A necropsy was then done on each of these rats (except those in group V) and the tissues preserved.

^a Exams performed by W. F. Keller, D.V.M., M.S. and associates, Diplomates, American College of Veterinary Ophthalmologists, Michigan State University, East Lansing, Michigan.

DRAFT**2. Tests Performed**

The following tests^a were performed:

Hematology: hemoglobin (HGB), hematocrit (PCV), erythrocyte count (RBC), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), total and differential leucocyte counts (WBC), estimated platelet count (PLT).

Serum Chemistry: alkaline phosphatase (Alk phos), blood urea nitrogen (BUN), glutamate pyruvate transaminase (SGPT), glutamate oxalacetate transaminase (SGOT), glucose (Gluc), total protein (TP), albumin (Alb), A/G ratio (calculated), globulin (calculated), total bilirubin (Tot. bili.), sodium (Na), potassium (K), chloride (Cl), calcium (Ca), inorganic phosphate (Phos), carbon dioxide (TCO₂), total serum cholesterol (Chol), creatinine.

Urinalysis: pH, specific gravity, glucose, protein, ketones, bilirubin, urobilinogen, microscopy of sediment.

6. Necropsy

A necropsy was performed on all surviving rats of the first 10 males and 10 females from each dose group on day 43 or 44 of the study. On days 92 or 93 the remaining rats were necropsied. Rats found dead were also necropsied. Interim and final sacrifice rats were anesthetized with CO₂ and exsanguinated by cardiac puncture. The cranial, thoracic and peritoneal cavities were opened and the contents examined macroscopically. The organs and tissues listed in section H were removed from each animal and preserved. Lungs were inflated with formalin via the trachea. Eyes with attached optic nerve from all

^a See Appendix C for clinical pathology methodology.

^b Protocol Change #1, effective 8/15/85; Protocol Change #2, effective 8/13/85.

^c Protocol Change #4, effective 9/10/85.

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rats killed at the interim and final sacrifices were preserved in a modified Zenker's fixative. The testes with attached epididymides from all male rats were preserved in Bouin's fixative. All other tissues were preserved in 10% neutral-buffered formalin. Feet were preserved with the tissues for positive identification of the rat.

Prior to fixation at the final sacrifice only,^a the following organs were weighed: brain, heart, liver, spleen, kidneys, testes with epididymides, and ovaries. After fixation, the adrenals and thyroids with parathyroids were weighed.^a For paired organs, the organ weight was the combined weight of right and left members of the pair. Organ/body weight ratios were determined for each tissue. No organ weights were taken on rats found dead.

H. Histology

The full tissue microscopic examination listed below was done on the control and high-dose rats, on one rat sacrificed in extremis, and on those found dead. Also, livers, hearts, and kidneys of low- and mid-dose rats, and all gross lesions seen at necropsy were examined microscopically.

As tissues were trimmed, the presence or absence of tissues and lesions was noted. The tissues were placed in Tissue Tek^{®b} cassettes that were labeled with study number, rat number and the cassette

^a Protocol Change #4, effective 9/10/85.

^b Lab Tek Division, Miles Laboratories, Inc., Naperville, IL 60540.

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number. They were then processed on a Fisher Scientific Histo-matic^a or on AO TP/8000.^b After processing, the tissues were embedded in paraffin using a Tissue Tek[®] embedding system. They were sectioned at 5-6 microns, mounted on numbered slides and stained with hematoxylin and eosin.

The following tissues were placed on sequentially numbered slides as follows:

Slide Number	Tissue
1	heart and attached aorta (a longitudinal section)
1	thymus
2	lung (sections from the caudal and left lobes)
2	trachea (a cross-section)
2	esophagus (a cross-section)
3	stomach (a section from the nonglandular esophageal area through the area of the cardiac glands into the area of the fundic glands and another section from the duodenum through the pyloric sphincter into the area of the pyloric glands)
3	salivary glands (sections of the sublingual and mandibular glands)
4	small intestines (a separate cross-section of the duodenum, jejunum and ileum)
4	colon (a cross-section)
5	liver (sections from the left and right lobes)
5	pancreas (a separate section in addition to sections commonly attached to the viscera)
5	spleen (a cross-section)
5	mesenteric lymph node
6	kidney (a cross-section of the right kidney)
6	urinary bladder (an entire cross-section)
7	adrenal (a section through the cortex and medulla of one adrenal)
7	pituitary
8	eye (with attached optic nerve)
9	thyroids and parathyroids
9	thoracic spinal cord (a cross-section) ^c
10	lumbar spinal cord (a cross-section) ^c

^a Fisher Scientific Products, 34401 Industrial Road, Livonia, MI 48150.

^b American Optical Scientific Instruments Division, Buffalo, NY 14215.

<u>Slide Number</u>	<u>Tissue</u>
10	brain (three sections including frontal cortex and basal ganglia, parietal cortex and thalamus and cerebellum and pons)
11	bone with marrow-femur
12	testis and epididymis (a cross-section of each)
12	ovary
12	uterus (a cross-section of one uterine horn)
12	cervix (a longitudinal section with uterine horns)
13	skin
13	mammary gland ^a
13	skeletal muscle (thigh) ^a
13	sciatic nerve
14, etc.	tissue masses and all other gross lesions

At the histologic examination, some lesions were graded, when necessary, using the following system: 1 = minimal, 2 = slight, 3 = moderate, 4 = severe, and 5 = extreme.

I. Statistics

The body weight, food consumption, clinicopathologic, and organ weight data were tested for homogeneity of variance by Bartlett's method (Steel and Torrie, 1980). If the data were found to be homogeneous, differences between control and treatment means were tested for statistical significance by the method of Dunnett (Dunnett, 1964). If the data were found not to be homogeneous, the method of Gill (modified Dunnett's) was employed (Gill, 1977).

J. Data Retention

All data including specimens and a copy of this report will be retained at Toxicity Research Laboratories, Ltd., 510 W. Hackley Avenue, Muskegon, Michigan 49444 for at least 5 years. Before any raw data is discarded, the sponsor will be notified to obtain permission.

^a Protocol Change #1, effective 8/15/85.

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III. Results

A. Test Material

The results of the analysis of samples analyzed by the Wastewater Treatment Facility and by ERCD are given in Appendix A. Stability and concentration were found to be acceptable.

B. Clinical Signs

The incidence of clinical effects is given in Table 1.

Treatment-related ataxia first appeared in the high-dose group during week 8. Ataxia and hypoactivity occurred infrequently during weeks 9 and 10. These signs increased to a weekly incidence of 32 and 29% for ataxia and hypoactivity, respectively, at week 11 and continued at approximately the same frequency during weeks 12 and 13. Onset of ataxia and hypoactivity was about 2-3 minutes after dosing and duration was less than one hour.

Other clinical signs observed did not appear to be directly related to treatment. Three rats died during the study. Two of these deaths were the result of the rubber catheter slipping off the metal dosing cannula. During week 4, a catheter lodged in the esophagus of a high-dose female and the rat died of apparent asphyxiation before the catheter could be removed. During week 7, a high-dose male swallowed a catheter. It was sacrificed two days later when it became apparent that the situation was adversely affecting the health of the rat. This accident and the occurrence of hypoactivity, salivation, labored respiration, and/or retching over a 3 day period in another high-dose

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rat account for the clinical effects observed in the high-dose group during weeks 6 and 7. A mid-dose male died during week 1. It began exhibiting hypactivity, emaciation, and labored respiration on day 4 and was found dead on day 6. Histopathologic evaluation of this rat will be discussed later in the report.

Dark urine and rales occurred in a high-dose male during week 8 following a cage related accident. This rat was normal in appearance within three days. During week 7, a 2 cm diameter tissue mass appeared in the left axillary area of one low-dose female and a 3 cm diameter mass appeared in the right axillary area of another low-dose female. Neither mass increased in size and both disappeared before study termination.

C. Body Weight, Weight Change and Food Consumption

The body weight, weight change and food consumption values are given in Table 2.

No treatment-related effect was present on body weight, weight gain, or food consumption. Statistically significant differences between control and treated group mean weight change and food consumption would occur sporadically, but no trend was observed and total body weight averages for control and treated groups were similar throughout the study.

D. Ophthalmology

The results of the ophthalmologic evaluations are given in Appendix B.

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An ophthalmoscopic examination was performed prior to initiation of dosing and all animals with ocular abnormalities were identified and discarded. Another ophthalmoscopic examination was performed during week 13. The pathology observed was considered to be within normal limits for the age, sex, and strain of the animal.

E. Clinical Pathology

Results of the clinicopathologic evaluation are given in Tables 3 through 7.

Only one alteration in clinical pathologic parameters occurred that was suggestive of a treatment-related effect. At the interim sacrifice, RBC ($p < 0.05$), PCV ($p < 0.01$), and HGB ($p < 0.01$) averages in the high-dose females were 5% less than the corresponding control averages. The RBC and PCV ($p < 0.05$) averages for the middle-dose females were also slightly (4% and 3%, respectively) below those of the controls. However, RBC, PCV, and HGB averages were similar for control and treated groups of males at the interim evaluation and for control and treated groups of both sexes at the final evaluation.

Other statistically significant differences between control and treated group averages occurred but they were small, occurred in one sex and at one evaluation only, and there was no dose response relationship. Thus, they were not considered to be treatment-related. They were: a lower ($p < 0.05$) cholesterol average in the high-dose males at the interim evaluation, a higher ($p < 0.05$) absolute neutrophil count in the middle-dose males at the interim evaluation, a

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higher ($p < 0.05$) relative segmented neutrophil count and a lower ($p < 0.05$) relative lymphocyte count in the low-dose females at the final evaluation, and higher ($p < 0.05$) urine pH values in the low-dose males at the interim and low-dose females at the final evaluations.

F. Observations at Necropsy

Observations made at necropsy are given in Table 8.

No treatment-related lesion was observed in gross necropsy at the interim or final sacrifices or of the rats found dead or sacrificed in extremis. The lesions present were those commonly observed in laboratory rats and they were present in control and treated groups at similar frequency or were one time occurrences. The enlarged uterine horns are related to the stage of the estrus cycle.

Three rats died during the study. No gross lesions were seen in rat # 224. Rat # 202 (which had a catheter in its stomach) had dark areas on the glandular mucosa of the stomach. In rat # 133 (middle-dose), the left lobe of the lung was red and the cranial and middle lobes were shriveled.

G. Organ Weights

Relative and absolute group mean organ weight values are given in Table 9.

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There was no apparent treatment-related effect on organ weight values. The only statistically significant difference between control and treated group averages was a slightly ($p < 0.05$) higher thyroid weight average in the high-dose males. No dose response relationship was present, as the absolute thyroid weights were similar for all three treated groups of males. Moreover, they were only 14% above the control average. Thyroid weight averages of the treated females were not above those of the controls. Thus, this difference appears to be a chance occurrence rather than a treatment-related effect.

H. Histopathology

The results of the histopathologic examination are given in Table 10 and Appendix D. The histoaccountability report is given in Appendix E.

No treatment-related lesion was observed at the histopathologic evaluation. The lesions that were observed were one time occurrences or were present in the control and treated groups at a similar frequency. The diffuse subacute lymphadenitis of the mandibular lymph node was visible grossly as red or enlarged lymph nodes. This is a commonly observed lesion in laboratory rats. The cause of death of the mid-dose rat (#133) that died during the study was determined to be a gavage accident since a perforated esophagus was found at the histopathologic examination.

IV Discussion

At the interim evaluation, HBC, PCV, and HGB averages in the high-dose

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females were 5% below control averages. The differences were statistically significant but the biological significance is questionable. All three parameters are closely related, so a decrease in the RBC count would be expected to result in a decrease in PCV and HGB values also. Moreover, the observed differences were small and no difference between these parameters was seen in males at the interim evaluation or between control and treated groups of either sex at the final evaluation. Thus, even if the decrease in RBC count (and hence, PCV and HGB) was a true treatment-related effect, it was small and transitory.

One mid-dose and two high-dose rats died during the study, but none of these deaths was due to administration of normal butanol. The two high-dose rats died because the rubber catheter slipped off of the dosing cannula during dosing. In one case (rat # 224), the catheter lodged in the throat and esophagus, thus cutting off air flow into the lungs. The rat died of apparent asphyxiation before the cannula could be removed. No gross or histologic lesion relating to the death of this rat was observed. The second rat (# 202) swallowed the catheter. It was sacrificed two days later, as the health of the rat was adversely affected by the presence of the catheter in its stomach. Gross necropsy revealed dark areas on the glandular mucosa of the stomach. This was seen histologically as focal necrosis.

Shriveled and red lungs were observed at gross necropsy of the middle-dose rat (# 133) that died. Histologic evaluation revealed pleuritis and edema in the lung and a perforated esophagus. Thus, death was the

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result of esophageal damage at dosing.

V Conclusion

Oral administration of normal butanol at 500 mg/kg/day produced ataxia and hypoactivity at a maximum weekly incidence rate of 32 and 29%, respectively. A slightly (5%) lower (compared to controls) red blood cell count (RBC), packed cell volume (PCV), and hemoglobin (HGB) concentration present in the 500 mg/kg/day dose group females at the interim evaluation only may have been treatment-related.

No treatment-related effect was observed at the 30 mg/kg/day or 125 mg/kg/day dose levels.

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VI References

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Gill, J.L. (1977). Journal of Dairy Science 60,444-449.

Steel, R., and Torrie, J.H. (1980). Principles and Procedures of Statistics, A Biometrical Approach 2nd ed., pp. 471-472. McGraw-Hill, New York.